Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ARTHRITIS ADVISORY COMMITTEE

December 1, 1998
Town Center Hotel
8727 Colesville Road, Silver Spring, MD

Members Present
Steven B. Abramson, M.D., Chair
Daniel J. Lovell, M.D., M.P.H.
Barbara C. Tilley, Ph.D.
Leona Malone, MSW
Frank Pucino, Jr., Pharm.D.
E. Nigel Harris, M.D.

FDA Participants
Robert DeLap, M.D.
John Hyde, M.D.
James Witter, M.D., Ph.D.
Mordechai Averbuch, M.D.
Lawrence Goldkind, M.D.
Douglas Throckmorton, M.D.
Josie Yang, Ph.D.
Sue Chih Lee, Ph.D.

Consultants
Matthew Liang, M.D., M.P.H.
Kevin R. McConnell, M.D.
Felix Fernandez-Madrid, M.D., Ph.D.

Guest Experts
Earl Silverman, M.D.
Denis McCarthy, M.D.

Members Absent
David Yocum, M.D.

Executive Secretary
Kathleen R. Reedy

These summary minutes for the December 1, 1998 meeting of the Arthritis Advisory Committee were approved on 6/4/99.

I certify that I attended the December 1, 1998 meeting of the Arthritis Advisory Committee and that these minutes accurately reflect what transpired.

Kathleen R. Reedy,
Executive Secretary

Steven B. Abramson, M.D.
Chairperson

The Arthritis Advisory Committee met on December 1, 1998 at the Town Center Hotel, 8727 Colesville Road, Silver Spring, MD to discuss NDA 20-998, Celebrex™ (celecoxib) Searle. Approximately 400 people attended the meeting. The Committee had been provided a background document from both the sponsoring company and the FDA review Division approximately 22 days prior to the meeting.

The meeting was called to Order at 8:00 am by Steven Abramson, M.D., Acting Chair, Arthritis Advisory Committee. The Meeting Statement was read by Kathleen Reedy, Executive Secretary of the Arthritis Advisory Committee. There were introductory comments by Robert DeLap, M.D., Director of ODE V and John Hyde, M.D., Acting Deputy Director of the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs.

The Searle Presentation consisted of:

Introduction: Dr. P.Needleman, Ph.D., Co-President Searle
Chief Scientist Monsanto
Non-clinical Overview: Dr. P. Isakson, Ph.D., Executive Director and
Senior Fellow COX-2 Technology
Clinical PK: Dr. A. Karim, Ph.D., ABCP Distinguished Scientist, Senior Director,
Clinical Pharmacokinetics and Bioavailability
Clinical: Dr. G. Steven Geis, Ph.D., M.D, Vice President
Celecoxib Clinical Development

The FDA Presentation was:

Introduction, Osteoarthritis, Rheumatoid Arthritis:
James Witter, M.D., Ph.D., Medical Officer,
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs
Pain: Mordechai Averbuch, M.D., Medical Officer,
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs
Renal: Douglas C. Throckmorton, M.D., Medical Officer,
Division of Cardio Renal Drug Products
GI: Lawrence Goldkind, M.D., Medical Officer,
Division of Gastro-Intestinal and Coagulation Drug Products
Pharmacology/Toxicology: Josie Yang, Ph.D.,
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs
PharmacoKinetics: Sue-Chih Lee, Ph.D.,
Office of Clinical Pharmacology and Biopharmaceutics
Conclusion: James Witter, M.D., Ph.D., Medical Officer,
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs

The Open Public Hearing followed.

1. SmithKline Beecham Pharmaceuticals' statement was presented by Robert H. Palmer, M.D., Group Director-Rheumatology Clinical Reserch and Development.
2. Whitehall-Robins, Stephen A. Cooper, DMD, PhD, Vice President Clinical and Medical Affairs, deferred to the next speaker.
3. Nonprescription Drugs Manufacturing Association made a statement delivered by

William Soller, Senior Vice President.

4. Bayer Corporation or the Aspirin Foundation of America statement was read by Thomas E. Bryant, MD, President.
5. Public Citizens Health Research Group made a statement delivered by Sidney Wolfe, M.D.

Discussion and Questions took place in the afternoon. The questions were answered as follows:
Efficacy

1. Should celecoxib be approved for the indications of the treatment of the signs and symptoms of OA (Yes - 9; No - 0) and RA (Yes - 9; No - 0).

2. For the Indication "Management of Acute Pain", the Division's usual requirement is replicated evidence of efficacy in at least two different types of pain models. Traditionaliy, one type should be a single-dose model (e.g. dental pain) while the other type should be a multiple-dose model (e.g. post-operative, dysmenorrhea, etc.) studying patients with short-term (usually several days) therapy. While the replicated dental pain studies in this NDA support the analgesic efficacy of celecoxib, the multiple-dose studies are inconclusive (failed studies). The trials in OA are felt to be only supportive of the analgesic acute efficacy of celecoxib. The Agency believes that additional data are needed to support the acute pain indication. Does the committee agree? If so, what additional evidence should be provided?
The opinions were mixed but concern for a blanket pain indication was unanimous. The consensus was that the studies were not sufficient for indication for a broad array of pain or any type of pain. Discussion of orthopedic pain and use in pediatrics as exclusions requiring additional study took place and there was consensus that musculo-skeletal pain could be included without further study.

Gastrointestinal

3. At prior AAC meetings on this subject, endoscopic studies have been viewed as surrogates of clinically meaningful endpoints. Given that celecoxib, in these endoscopic studies, has demonstrated consistent statistical superiority to only two of the three NSAIDs studied, what comparisons (if any) should be allowed in the labeling between celecoxib and these NSAIDs? Can these data be extrapolated to make comparisons between celecoxib and all other NSAIDs as well?
There was extended discussion regarding the concept of celecoxib as an NSAID; that NSAIDs are not comparable with one another, therefore not comparable to the new product, celecoxib. A discussion of endoscopic studies as valuable clinical data but not a surrogate nor a predictor of outcome, nor usable as they decrease the power of the studies. Endoscopy does not address anti platelet effect of celecoxib, h. Pylori, and other issues.

4. An underlying concept of the celecoxib development program has been that COX-2 selectivity would provide enhanced GI safety. While the celecoxib studies completed to date suggest that endoscopically diagnosed ulcers may occur less frequently with celecoxib treatment compared to NSAID comparators, studies completed to date have not included definitive comparisons of clinically significant GI adverse events. Is the NSAID warning template still appropriate, pending completion of appropriately powered trials to assess the incidence of significant GI events with celecoxib compared to one or more NSAID products? Or should

qualifications be made to the NSAID GI warning template, while noting the limited experience with the new molecular entity?
The Committee consensus was that the existing class labeling is informative but the celecoxib labeling should be a qualified or modified version reflecting the studies to date affecting the organ systems studied. Conservative labeling is recommended without comparability or equivalence to NSAIDs, but possibly comparable to placebo.

5. NSAID labeling currently recommends against concurrent use of aspirin and NSAIDs. In view of the apparent lack of antiplatelet effect and the limited data from controlled endoscopy studies, what recommendations, if any, should be made concerning use of prophylactic low dose aspirin concurrently with celecoxib?
Current NSAID labeling regarding concurrent use of prophylactic low dose aspirin is sufficient for use with celecoxib.

Questions 6-10 were not answered specifically as the discussion had covered the issues.
Renal
6. The sponsor and the FDA have agreed that the overall renal effects of celecoxib, including the incidence of peripheral edema and other renal adverse effects, are similar to those of currently approved NSAIDs.
    a. Do you agree with this assessment?
    b. How should any conclusion be reflected in labeling?
7. The NDA did not collect data on serum bicarbonates. Given the other laboratory abnormalities noted in the NDA:
    a. Should additional safety studies be required?
    b. How should this absence be reflected in labeling?
Other Issues
8. Information obtained from pharmacokinetic studies indicates that elderly subjects have a 40% increase in Cmax and a 70% increase in AUC. The FDA proposed label calls for initiating therapy with the lowest dose and titrating up slowly. Does the committee agree?
9. Celecoxib is almost entirely dependent upon hepatic metabolism (via P450 2C9). In patients with mild or moderate hepatic insufficiency should the dose or dosage regimen be altered?
    Mild hepatic insufficiency (plasma celecoxib levels 1.3-1.4x normal)
    Moderate hepatic impairment (plasma celecoxib levels > 2x normal)
10. At the present time there are no studies in subjects with severe hepatic failure. Should the sponsor be required to do studies which monitor both pharmacokinetics and clinical outcome (i.e. adverse events) prior to making labeling recommendations for this patient population?

11. Please provide recommendations for any Phase 4 studies for Celebrex™.
Pediatric studies
Bone studies.

The meeting adjourned at 5:45 pm.

Kathleen Reedy, Executive Secretary
Arthritis Advisory Committee